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March 10, 1999

Cilag Comments on Draft FDA Guidance
BACPAC I: Intermediates in Drug Substance Synthesis
Docket No. 98D-0994

Gentlemen,

Cilag considers BACPAC I as providing some regulatory relief with regard to changes up to and including the final intermediate step. Our concern with BACPAC I is the use of CBE for process changes in early steps of the synthesis. The issue is that for a DMF there is no mechanism for CBE without an update to the(each) NDA that would be affected. It is our position that change should be evaluated as close as possible to the synthesis step where the change has been made. If the change occurs prior to the final intermediate and there is no change in impurities at the final intermediate, we feel that the filing should be an annual report. We feel that this is essential to provide regulatory relief.

The guidance contains sufficient detail that regulatory decisions are now much clearer for post-approval changes made in early synthetic steps. The general approach of comparing the equivalence of material pre- and post-change represents a rationale, scientific method for evaluation of the impact of a given change. The filing requirements in the draft guidance reflect the results of this evaluation and provide considerable regulatory relief from those currently delineated in 21 *CFR* 314.70. Significant benefit to industry is also realized with the ability to demonstrate equivalence based on impurity profile at synthetic intermediates after the change, without always requiring evaluation of the API (including physical properties or stability).

It is acknowledged by the pharmaceutical manufacturing firms that for many older processes, analytical methodology is not currently in place for full characterization of the impurity profiles of the synthetic intermediates. In such cases, the development and validation of adequate analytical methods for quantifying existing and new impurities may be considered too costly to take advantage of the regulatory relief

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offered by evaluation of changes at process intermediates. For recent and future filings, more detailed in-process specifications and test methods are available and evaluation of changes will be effectively carried out early in the synthesis.

General Comments

The following discussion briefly summarizes the key issues from Cilag's review of this draft guidance. A detailed list of comments (with reference to specific line numbers) is also provided.

We understand the changes covered by BACPAC I to be within the stated intent of 21 *CFR* 314.70(a), which would encompass changes in the information filed in the approved application. For example, details regarding equipment used in early steps and scale of manufacture are not always included in regulatory filings. It is recommended that the section on scale changes be dropped, since the majority of scale changes are driven by changes in equipment or site, which are handled in other sections of the guidance.

One area of concern is the level of documentation requested in support of changes. In some areas, the required data and information is greater than that provided in an NDA filing. It is the experience of Cilag companies that analytical methods for raw materials and intermediates are briefly summarized and no accompanying validation data is provided in original NDA filings. The in-process methods are validated for their intended use and the detailed validation data would be available for inspection. The requirement of certificates of analysis for raw materials and starting materials is another example of additional detail not typically provided. A batch data summary for the relevant materials should meet the requirement. In the case of the redefinition of an intermediate as a starting material, the list of sources and the change-control protocol are considered GMP considerations that should not be included in a filing, but rather should be available for an inspection.

The extent of the comparison to demonstrate equivalence of pre-change (10 batches) and post-change (3 batches) material has been clearly indicated. For certain low volume or recently approved drug substances, the historical database may not include ten commercial scale batches. In such cases, the firm should be allowed to provide justification for the use of less than ten historical batches or be permitted to use pilot scale development batches. The option of using more than ten historical batches in the comparison has been recommended for inclusion in the text. If the use of statistical limits is not feasible, a direct comparison of data should be permissible. Where limits have been approved for specific impurities in an intermediate, meeting these limits would demonstrate equivalence.

When the assessment extends to the drug substance, the need for physical property evaluation should not include cases where impurity profile equivalence is

demonstrated at the crude drug substance prior to a step involving complete dissolution of the material.

Given that this guidance only deals with changes up to the final intermediate, some changes in the indicated type of filings are suggested. An Annual Report is suggested for site changes to a site that is currently manufacturing/testing a FDA-approved product/intermediate, which uses a similar process or technology, and that has a current satisfactory GMP inspection by FDA or a governmental authority recognized by FDA. For sites that would not meet these criteria, a prior approval supplement would be used to initiate an inspection. If the only change made is a change in specifications driven by a method change, filing in an Annual Report is considered appropriate. Similarly if a change in specifications of the final intermediate is driven solely by a method change, this specifications change should fall under BACPAC I.

Specific Comments

The following represent specific comments on lines of the draft guidance document. Comments have been grouped as major, minor or clarification through changes in wording. When a comment applies to a section that is repeated several times in the document (i.e. Test Documentation), the comment is shown with the first line of text that it refers to and subsequent lines of the same text are referenced. Text that is suggested for addition is generally underlined to differentiate it from existing wording.

I. Introduction

Major Comments

Line 16 It is recommended that the specifications for the final intermediate be included, particularly since analytical method changes that could drive a change in final intermediate specifications are included. This would be analogous with inclusion of drug substance specifications in BACPAC II.

Clarification

Lines 32-39 Clarification of this paragraph regarding the "changes to an approved application" is needed, since changes could be made for items on which the approved application is silent. The text in 21 *CFR* 314.70(a) states:
The applicant shall notify FDA about each change in each condition established in an approved application beyond the variations already provided for in the application.

II. General Considerations

Major Comments

Line 120-121 Replace the sentence: "When new methods are developed for this purpose, validation data should be provided" with New methods that are developed should be appropriately validated for the intended purpose and the validation data should be available for inspection.

Clarification

Line 74 ...all applicants authorized to reference the master file should be notified of changes that need to result in a CBE or PAS to the application.

Line 77 Add drug substance applications.

Line 88 Add small changes in drug substance impurities.

Line 89-91 Rephrase as:

For such drug products ~~in which stability problems may potentially occur~~, the first commercial *batch* of drug product made with postchange drug substance may be included in the firm's stability testing program.

Line 95-96 Isomers may be present in a drug substance as either low level isomeric impurities or 1:1 racemic mixtures. In the case of low level isomeric impurities, the change could result in a decrease in the level of the undesired isomer and still be considered equivalent or better.

Suggested revision: demonstrate equivalence (e.g. chirality). ~~For example, if the drug substance is a mixture of isomers, then the same quantitative mixture should be obtained after the change.~~

A. Equivalence of Impurity Profiles

Minor Comments

Line 124 Modify "ten or more premodification ~~commercial~~ batches

Line 128 Modify "~~at least~~ three"

Line 129 It is suggested that the demonstration of equivalence may take place at an *in situ* intermediate if appropriate justification is provided and that the line should read isolated (*in situ*, if appropriately justified).

Line 132 To comply with ICH, delete "at or" since impurities above 0.1% are the issue.

Line 137 Modify to include any specifications for specific impurities that have been filed for an intermediate:
Existing impurities, including residual organic solvents, if relevant, are within the stated limits or, if not specified, at or below the upper statistical limits of historical data.

Line 139 Modify to include any specification for total impurities that has been filed for an intermediate:
Total impurities are within the stated limits or, if not specified, at or below the upper statistical limit of historical data.

Line 159 Include the option that *in situ* intermediates may be used to demonstrate equivalence with appropriate written justification

Clarification
Line 103 Substitute may for "should also".

Line 115-116 Suggested revision: ~~When it is not feasible to evaluate impurities in intermediates or equivalence cannot be~~ If equivalence is not demonstrated at these stages,

Line 131 After "1. An intermediate:" add The applicant may evaluate any subsequent intermediate or the final API to confirm impurity levels comply with this guideline.

Lines 173-177 The text is confusing. It might be clearer to indicate under "Manufacturing Process Changes" that no additional purification steps for the final intermediate beyond those already filed may be added to achieve equivalence.

B. Equivalence of Physical Properties

Major Comments
Line 191 If equivalence is demonstrated at the crude drug substance stage then physical property evaluation should not be required. Suggest change from "prior to or at the final intermediate" to "prior to the final API".

Line 200 Add the underlined text:
Conformance to historical particle size distribution profile, when acceptance criteria do not exist.

A. Site, Scale, and Equipment Changes

1. Site Changes

Major Comments

Line 234 Include information regarding the current status of site for manufacturing/testing a FDA-approved product/intermediate which uses a similar process or technology, and if the site has a current satisfactory GMP inspection by FDA or a governmental authority recognized by FDA.

Line 241 Indicate brief description of analytical methods, since for intermediate testing only a short summary of type of method and conditions is typically provided in the NDA. (also applies to lines 287, 372, 415, 454 and 508)

Lines 243-245 For in-process tests or tests on intermediates, validation data is not routinely included in the NDA filing. It is suggested that the sentence "Validation data should be provided for new test methods and also for existing methods if their use is being extended beyond their original purpose" be replaced with These methods should be appropriately validated. This evaluation will not necessarily result in additional specifications or testing requirements. (also applies to lines 289, 333, 348, 375, 417, 456 and 511)

Lines 259-260 The requirement for a certificate of analysis for each outsourced intermediate could also be addressed by a compilation of batch data. (also applies to lines 259, 305, 391, 439, 477 and 534)

Lines 262-272 It is suggested that an Annual Report be the filing for a change to a site that meets the following criteria:
-currently manufacturing/testing a FDA-approved product/intermediate, which uses a similar process or technology
-current satisfactory GMP inspection by FDA or a governmental authority recognized by FDA.
If the site does not meet the above criteria then a prior approval supplement would be the filing.

Clarification

Line 227 Change "single facility" to single campus.

Line 257 Substitute may for "should". (also applies to lines 303, 389, 437, 475 and 532)

2. Scale Changes

Major Comments
It is recommended that scale changes not be included as a separate category, since other changes handled elsewhere in this guidance (i.e. equipment or site) typically accompany scale changes.

3. Equipment Changes

Clarification
Line 311 Modify to "when equipment (as specified in the filing) changes alone are made".

Line 319 Change "previously used" to "previously filed".

Line 323 Add the phrase "significant change of equipment from that previously filed.

Line 325 Delete the final phrase "and documented as described for scale changes" since we have suggested deletion of that section.

A. Specification Changes

Major Comments
Line 328 As discussed in the introduction, changes to final intermediate specifications that are driven by method changes alone should be included under BACPAC I.

Line 348 Delete "and validation data" since these are in-process test methods for intermediates.

Lines 349-350 and line 391 Inclusion of COA's for raw materials and solvents is not considered necessary based on the early stage of the synthetic process. Batch data for intermediates should appropriately address this item.

Line 354 and line 395 If the only change made is a specification change, then reporting by Annual Report is considered appropriate. If another type of change were also made, then evaluation of equivalence would need to be demonstrated and the designated filing mechanism used.

Minor Comments

Line 330 Not many compendial monographs exist for compounds that would be used as synthesis intermediates.

Line 370 Delete physical properties testing for assessment of intermediates.

B. Manufacturing Process Changes

Major Comments

Line 442 For manufacturing process changes made prior to the isolated final intermediate, reporting by an Annual Report is suggested for all cases where impurity profile equivalence is demonstrated before or at the final intermediate. For those changes in which the evaluation is carried out on the drug substance, a Changes Being Effected supplement is the suggested filing.

Line 480 Likewise, for changes in the route of synthesis made prior to the isolated final intermediate, reporting by an Annual Report is suggested for all cases where impurity profile equivalence is demonstrated before or at the final intermediate. For those changes in which the evaluation is carried out on the drug substance, a Changes Being Effected supplement is the suggested filing.

Lines 501-502 "A list of sources of the redefined starting material" is considered a GMP item that should be available for inspection, but not be included in a filing to the agency.

Lines 503-505 The change-control protocol is another GMP requirement that should be available during an inspection, but should not be required to be filed with the agency.

Line 534 COA's or batch data for a redefined starting material are suggested.

Minor Comments

Line 424-5 Suggested revision: The level of the new solvent in the drug substance should assure that the drug substance conforms to ICH Q3C.

Line 427 Delete "Option 1". (also applies to lines 461-466 and 517-522)

Clarification

Line 413 Delete physical properties testing for assessment of intermediates.

Lines 420-421 If equivalence of the impurity profile is established prior to the drug substance (even at the stage of crude API) then no physical properties testing of the drug substance should be necessary. (see comment on line 191)

Line 437 Replace the word "should" with "may".

Attachment B – Glossary of Terms

Line 571 Replace "processed" with produced.

Line 576 Add "Drug Substance (API)".

Line 582 Add "covalent bond formation and/or cleavage".

Line 585 Clarify "The step that includes solution".

Line 589 Revise to "impurities or physical attributes for API from 10 or more batches".

Line 591 Revise to "~~(The appropriate review division(s) should be contacted for concurrence~~ Written justification should be provided in those ~~rare~~ instances".

Lines 607-608 Delete the sentence "The isolation or purification procedure should be part of the validated process."

Line 633 Replace "drug substance" with material, since in BACPAC I many evaluations cover intermediates.

Lines 640-643 Align term and its definition with ICH Q7A (in working group) as follows:
API Starting Material: A material used in the production of an API which is itself or is incorporated as a significant structural fragment into the structure of the API. A starting material may be an article of commerce, a material purchased from one or more suppliers under contract or commercial agreement, or it may be produced in-house. Starting materials are normally of defined chemical properties and structure.

Sincerely,

CILAG AG

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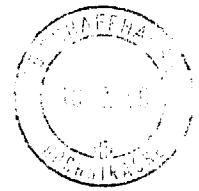

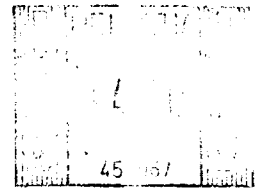

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